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Identification and Molecular Confirmation of a Small Chromosome 10q Duplication [dir dup(10)(q24.2→q24.3)] Inherited From a Mother Mosaic for the Abnormality

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We describe a family in which two siblings exhibited developmental delay, reduced muscle tone and mild muscle weakness. Cytogenetic evaluation demonstrated that both children had a tandem duplication of a small portion of the long arm of chromosome 10 [46,XX or XY,dir dup(10)(q24.2→q24.3)], inherited from their clinically normal mother, who was found to be mosaic for the duplicated chromosome 10. Fluorescence in situ hybridization approaches, including total chromosome painting and the use of regional specific cosmid probes, were used to confirm the chromosome 10q origin of the duplicated material. This is the smallest confirmed duplication of this portion of chromosome 10 reported to date.

KEY WORDS: dup(10q) syndrome, cytogenetics, partial chromosome duplication, mosaicism

INTRODUCTION

The degree of mental retardation and the incidence of malformations which are associated with a chromosome abnormality usually correlate positively with the size of a duplicated or deleted chromosome segment. It is generally accepted that duplicated regions give rise to less severe clinical phenotypes than comparable deletions.

Partial trisomies of distal 10q caused by meiotic adjacent-1 segregation in a parental balanced translocation carrier have occurred frequently enough to permit description of a recognizable syndrome of distal 10q partial trisomy with many dysmorphic findings and frequent major malformations [reviewed in Yunis and Sanchez, 1974; Klep-de Pater et al., 1979; Tomkins et al.,1983; Neely et al.,1988; Jones, 1988]. Tandem duplications in 10q have been reported much less frequently. Proximal 10q tandem duplications have been reported in three children with identical or very similar duplications (10q11→q22) [Vogel et al., 1978; Fryns et al., 1987; de Michelena and Campos, 1991] and in two males with smaller duplications in the same region (10q21→q22) [Koivisto et al., 1981; Reinthaller, 1985]. To our knowledge, only two tandem duplications in distal 10q have been reported, 10q22→q25 [Pison et al., 1982] and 10q24→q26 [Tomkins et al., 1983].

We describe here a family with two siblings with developmental delay and neurological findings. Both siblings carry a tandem duplication involving chromosome 10q [46,XX or XY,dir dup(10)(q24.2→q24.3)] inherited from their mother, who was found to be mosaic for the abnormality. The patients did not exhibit the pronounced dysmorphic findings commonly associated with partial trisomy 10q syndrome. These are the first reported cases of a tandem duplication involving this specific small region of chromosome 10.

CLINICAL REPORTS

Case 1

A 6-year-old Latin-American boy (Fig. 1) with a history of global developmental delay and hypotonic weakness since birth was referred to a neurologist by his school. He was born by caesarean section (for cephalopelvic disproportion) to a healthy, gravida 1, normal mother after a normal, full-term pregnancy. At birth he weighed 7 lb 4 oz and was described as a "floppy" and "cranky" baby. His developmental milestones were delayed as follows: he did not lift his head until 6 months, did not sit until 12 months, did not walk until 2 years, and was not toilet-trained until 4 years. At 24 months of age he spoke only a few words and could not identify

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Fig. 1. The siblings reported as cases 1 and 2 with their mother.

colors until 4 years. His medical history was otherwise unremarkable.

On physical examination, his weight and height were at the 95th percentile and head circumference at the 75th percentile. The general examination was unremarkable. Neurological examination revealed an alert child who was able to interact with the examiner. He had a nasal voice with a mild degree of dysarthria, having difficulty in pronouncing "r" and "s" and in repeating words that had more than three syllables. Cranial nerve function and his sensory system were normal. Deep tendon reflexes were decreased. Although muscle bulk was normal, diffuse hypotonia and mild to moderate weakness in the neck and shoulders were noted. Electromyography and nerve conduction studies were normal, as was magnetic resonance imaging (MRI).

Psychometric testing at age 4 years using the Stanford-Binet test showed an I.Q. of 74 (borderline). A developmental activity screening inventory showed a score of 81 (normal 85–115). The preschool language scale demonstrated an auditory comprehension quotient of 73 and a verbal acquisition quotient of 54 with a combined language quotient of 63. The mental age at 4 years was considered to be 3 years, 2 months.

Case 2

This 28-month-old Latin-American female sibling of case 1 was born by caesarean section to a healthy, gravida 2, normal mother after a full-term pregnancy (Fig. 1). She weighed 6 lb 10 oz and required oxygen in the intensive care nursery for 10 days. Similar to her brother, she was described as floppy from birth and had delayed developmental milestones. She did not lift her head until 6 months, did not sit until 12 months, did not crawl until 18 months, and did not walk until 2 years. At 22 months, she spoke only a few words. In addition, at age 18 months she had generalized tonic-clonic seizures lasting 1–2 minutes each with hyperthermia (temperature 102°F).

Physical examination showed weight, height, and head circumference to be at the 50th percentile. The general examination was unremarkable except for hypertelorism and diffuse eczema. Neurological examination showed an alert child who was able to say only a few words and did not follow commands well. Her cranial nerve function and sensory system were normal but, unlike her brother, her deep tendon reflexes were increased. Reduction in both muscle tone and muscle power were noted diffusely, which were similar results to those found in her brother.

Psychometric examination performed at 28 months using the Bayley Scales of Infant Development showed a mental age equivalent score of 16 months, with a mental developmental index of 50, placing cognitive development in the delayed range. A basal level was attained at 13.4 months, with scattering to the 19.1 month level. MRI of the head and electroencephalogram were normal.

The parents were examined. Both exhibited normal intelligence and normal neurological function.

METHODS AND RESULTS

Chromosome studies were performed from peripheral blood specimens using standard cytogenetic procedures. Cultures were treated with methotrexate for prometaphase analysis [Yunis, 1976].

GTG-banding [Seabright, 1971] demonstrated a duplication of at least part of band 10q24.2 and almost all of band 10q24.3 (Fig. 2) in all twenty metaphase cells from each of the siblings (cases 1 and 2). Cytogenetic analysis of paternal lymphocytes showed a normal male karyotype. Chromosome analysis of maternal lymphocytes showed mosaicism, with a normal female karyotype in 90% of lymphocyte metaphase cells, and an abnormal cell line with a similar duplication of chromosome 10q24.2→q24.3 in 10%.

Fluorescence in situ hybridization (FISH) was performed to confirm the chromosome 10 origin of the duplicated material. The chromosome 10-specific total

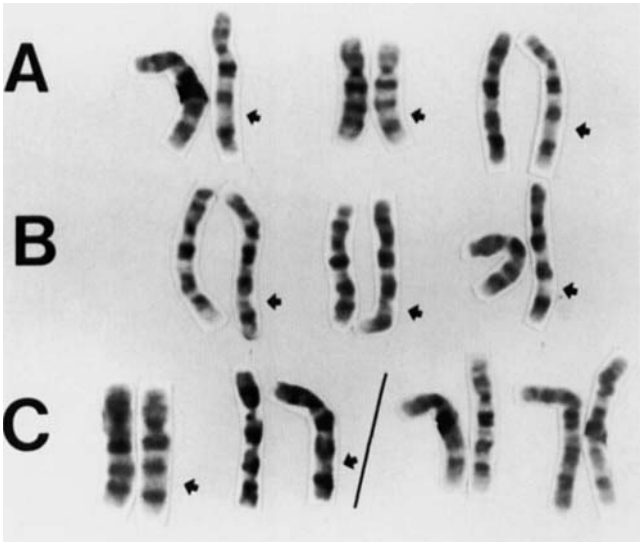

Fig. 2. Representative GTG-banding of chromosome 10 in metaphase cells derived from case 1 (**A**), case 2 (**B**), and the mother of these patients (**C**). The arrows indicate the duplicated band. The mother was mosaic as demonstrated by the presence of metaphase cells which did (left) or did not (right) exhibit the duplicated chromosome 10.

chromosome painting probe cocktail (Oncor, Inc., MD) was used to paint maternal and proband metaphase cells. Hybridization and detection reagents and conditions were as recommended by Oncor. Following hybridization to metaphase cells from cases 1 and 2, signal was detected on a single pair of chromosomes, indicating that translocation of chromosome 10 material to another chromosome had not occurred in the generation of this abnormal karyotype. More importantly, the probe painted the full length of both the normal and duplicated 10 chromosomes, a result consistent with the interpretation that the duplicated material was of chromosome 10 origin. These results are illustrated in Figure 3B.

In addition to chromosome painting, six chromosome 10-specific cosmids previously mapped to bands 10q24.1-q25.3 [Zheng et al., 1994] were used as probes to confirm the limits of the duplicated region. The ideogram in Figure 4 illustrates the map location of the six cosmids used. Cosmid DNAs were biotinylated with the BioNick Kit (GIBCO/BRL) following the directions of the manufacturer, with the exception that labeling reactions were for 16 hr at 16°C. Each probe (100 ng) was precipitated and resuspended in 15 μl of hybridization solution containing 50% formamide, 100 μg/ml dextran sulfate, 1× SSC, and 0.1% Tween 20. Hybridization to metaphase cells prepared from each sib was carried out at 37°C for 16 hr. Biotin was detected with fluoresceinated avidin and amplified 1× with biotinylated anti-avidin as previously described [Lichter et al., 1988]. Chromosomes were counterstained with DAPI (0.4 μg/ml) in antifade (1 mg/ml p-phenylenediamine dihydrochloride, 20 mM Tris pH 8.0, 80% glycerol) and results were visualized and photographed on a Zeiss Axiophot Fluorescence Photomicroscope using a Zeiss triple-pass filter and 400 ASA film.

As presented in Figures 3A and 4, four of the six cosmid probes (CRI-JC2008, CRI-JC2052, CRI-JC2119, and CRI-JC2056) produced a single hybridization signal on one chromosome 10 and a duplicated signal on the homologue. The two remaining probes (CRI-JC2010 and CRL-JC2199) yielded single signals on both homologues. These data confirm the duplication of chromosome 10q material and are consistent with the original cytogenetic observations which defined the abnormal karyotypes as 46,XX or XY,dir dup(10)(q24.2→q24.3).

DISCUSSION

Most reported cases of partial trisomy of distal 10q have trisomy of the segment 10q24→qter and result from segregation of a balanced translocation in a parent; therefore, these cases also have monosomy of a small portion of some other chromosome. The recognizable phenotype is apparently caused primarily by the trisomic 10q segment and includes severe mental retardation and craniofacial dysmorphisms of microcephaly, prominent forehead, highly arched eyebrows, short palpebral fissures, microphthalmia, blepharoptosis, broad and depressed nasal bridge, and a bow-shaped mouth with prominent upper lip. Other common ab-

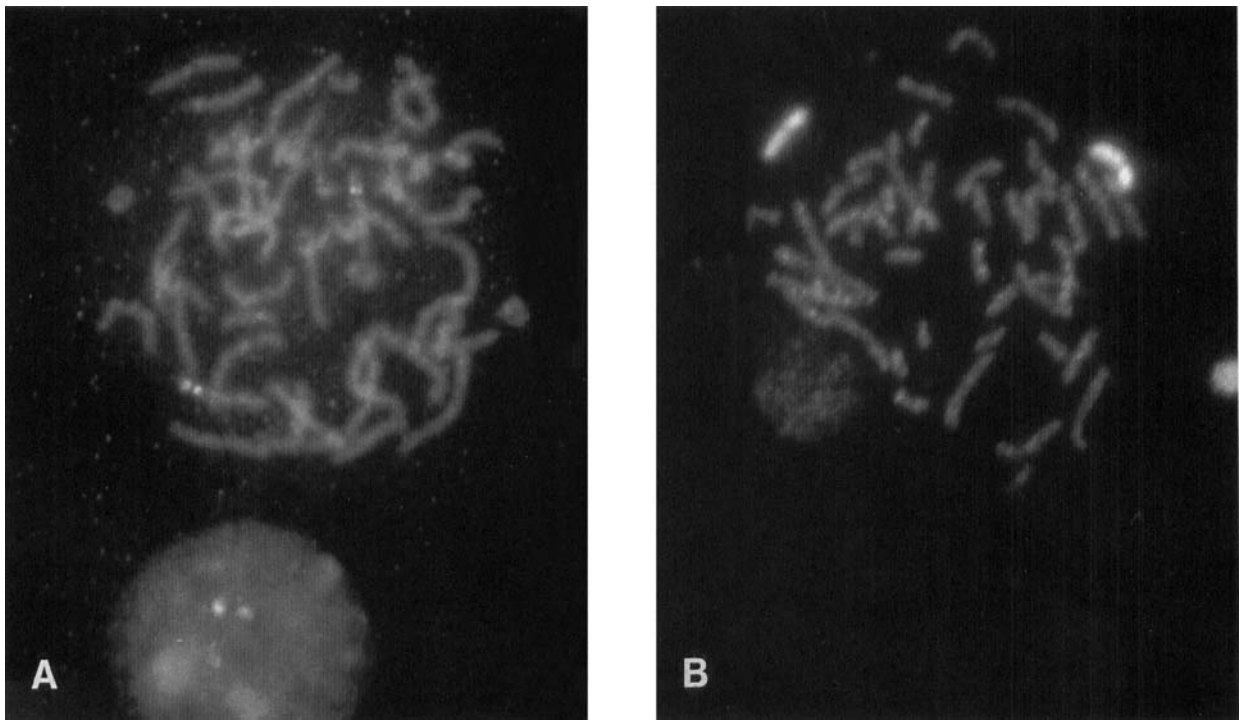

Fig. 3. FISH analysis of the 10q duplication in metaphase cells. **A:** Representative FISH results with cosmid CRI-JC2052 illustrating a duplication on one homologue of chromosome 10. **B:** Hybridization to a metaphase cell from case 2 with total chromosome 10 painting probes produces signal along the full length of each chromosome 10, and only on chromosome 10.

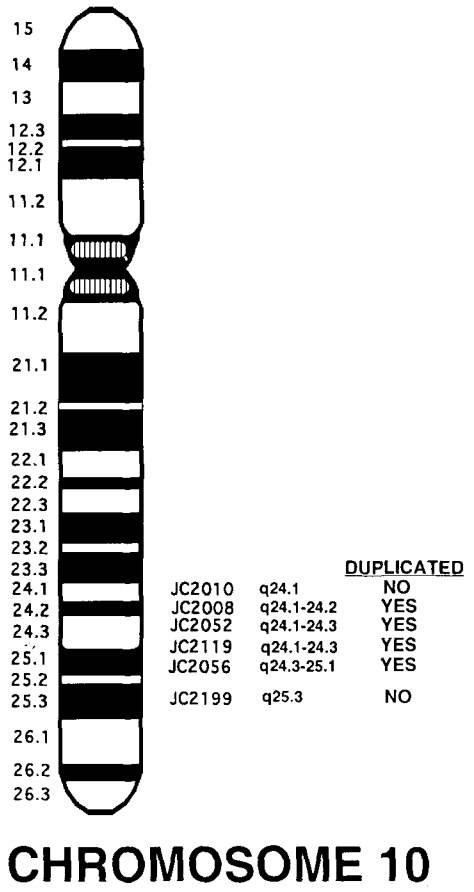

Fig. 4. Chromosome-specific cosmid probes used to confirm the chromosome 10 origin of the duplicated band shown in an ideogram illustrating the previously assigned map locations of the CRI cosmid probes used in the present study, and a summary of the results obtained.

normalities include growth retardation, cardiac, renal, and/or skeletal malformations, and abnormalities of the hands and feet [Tomkins et al., 1983; Jones, 1988].

Cases of "pure" partial trisomy of distal 10q caused by tandem duplication or by insertion of a segment of distal 10q into another chromosome can define phenotypes associated with 10q excess alone, uncomplicated by concurrent deficiency of part of another chromosome. The case of tandem duplication of 10q24→q26 reported by Tomkins et al. [1983] and the cases of partial trisomy resulting from insertion of 10q24→q26 reported by Back et al. [1979] and by Johnson and Sutliff [1994] confirm that the distinctive phenotype is indeed associated with trisomy for the segment 10q24→q26.

The siblings reported here have duplication of only a small part of the 10q24→q26 segment and have none of the characteristic phenotypic abnormalities associated with trisomy of the larger segment. They have only mild developmental delay and are not dysmorphic, nor do they have any known malformations. To our knowledge, the only other reported liveborn cases with "pure" trisomy for only a portion of this 10q24→q26 segment are two adult relatives with trisomy of 10q24.2→q25.3 resulting from segregation of a familial balanced insertion; their only reported abnormalities were mild mental retardation, speech difficulties and (in one) aggressive behavior, although dysmorphic findings were not evaluated [van den Vooren et al., 1984]. A tandem duplication of 10q22→q25 in a 21-week fetus with downslanting palpebral fissures and cardiovascular malformations was also reported by Pison et al. [1982].

These findings, in conjunction with the present study, confirm the suggestion of Taysi et al. [1983] that duplications involving the more distal segment of the region are likely to be associated with the more prominent dysmorphic features of partial trisomy 10q syndrome.

Peripheral blood lymphocytes from the mother of the probands in the present study demonstrated mosaicism for the duplicated chromosome which was present in 10% of the cells examined. The fact that both of her two children carry the duplication indicates that this abnormality may be fixed at a higher frequency in reproductive tissues. Representation in other tissues is unknown. However, no clinical abnormalities were noted for the mother.

Inheritance of cytogenetic abnormalities from a parent who is mosaic for the anomaly is presumably rare. However, a number of such cases have been published. For example, parental mosaicism has been described as a cause of Down syndrome. Kaffe et al. [1974] described a family with maternal mosaicism for chromosome 21 in which the mother gave birth to two children with trisomy 21 Down syndrome. Priest et al. [1977] evaluated 100 consecutive cases of Down syndrome and performed cytogenetic evaluation of less than half of the parents; nevertheless, these cases revealed two mothers to be mosaic for the Down syndrome karyotype in either fibroblasts or peripheral blood lymphocytes.

Familial inheritance of a ring chromosome from a mosaic parent has also been described. Matalon et al. [1990] reported a mother with a mos46,XX,r(14)/45,XX, t(14q21q) karyotype who gave birth to two abnormal boys with seizures, mental retardation, and 46,XY,r(14) karyotypes. Jenderny et al. [1993] reported a family in which a proband with a 46,XX,r(18) karyotype inherited the r(18) from her phenotypically and mentally normal mother who had a mos46,XX/47,XX,r(18) karyotype.

Recently, Zori et al. [1993] reported a family in which a child with Smith-Magenis syndrome and the karyotype 46,XY,del(17)(p11.2p12) inherited his abnormal karyotype from his mother, whose karyotype was mos46,XX/46,XX,del(17)(p11.2p12). The mother had normal intelligence and minimal findings of Smith-Magenis syndrome.

Abnormal karyotypes with isochromosomes have also been inherited from mosaic mothers. Siblings with i(21q) Down syndrome or 47,XX,+i(21p) inherited from a mosaic mother with two abnormal cell lines were reported by Bartsch et al. [1993] and a child with 47,XX,+i(18p) who inherited her abnormal karyotype from her mosaic 46,XX/47,XX,+i(18p) mother was reported by Abeliovich et al. [1993].

The only reported case known to us of a tandem duplication inherited from a mosaic parent, similar to our family, is a duplication of 11q23-qter in a dysmorphic child inherited from his mosaic mother [Pfeiffer and

Schutz, 1993]. Unlike our family, however, the mosaic mother in that family had mild mental retardation.

Collectively, the above examples and the present case illustrate that transmission of an abnormal chromosome from a mosaic parent may be more common than is currently realized. While it is not feasible to perform cytogenetic evaluation routinely on all parents solely to identify mosaicism, these results reemphasize the contribution of this phenomenon to clinical cytogenetics.

High-resolution cytogenetics in the present study revealed the duplication as 10q24.2→q24.3. Map locations [McKusick, 1994] of some 20 genes are included in the region duplicated in our patients. The contribution that an extra copy of one or more of these genes makes to the phenotype of the affected siblings is not clear.

Molecular cytogenetics studies were used to confirm the chromosome 10 origin of the duplicated material. The FISH results with chromosome 10 cosmid probes were used to help define the limits of the duplication. As illustrated in Figure 4, the cosmid probes duplicated in the probands (CRI-JC2008, CRI-JC2052, CRI-JC2119, CRI-JC2056) have been previously mapped with a resolution that defines a region at a maximum of 10q24.1→q25.1 and at a minimum of 10q24.2→q24.3. The latter is directly in agreement with the high-resolution cytogenetic findings, providing an important confirmation of the origin of the duplicated material. Additionally, the data presented confirm the map locations recently reported for these cosmid probes [Zheng et al., 1994]. Given that probes CRI-JC2008 and CRI-JC2052 are duplicated while CRI-JC2010 is not, implies that the latter represents the most proximal of the three probes. The future use of similar probes should prove helpful in efforts directed at characterizing cytogenetic abnormalities associated with specific clinical phenotypes.

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